D9

49. (New) The method of claim 48, wherein detecting is accomplished by measuring intracellular calcium levels in the host cell.--

add E3

REMARKS

By this Second Supplemental Preliminary Amendment, the specification and claim 16 are amended, claims 19, 25, and 26 are cancelled, and new claims 38-49 are added. Currently, claims 16 and 38-49 are pending in this application.

The specification is amended to replace the Sequence Listing with a corrected version, to include Sequence Identifiers in accordance with the new Sequence Listing, to conform it to current PTO practice regarding explicit recitation of nucleic acid and amino acid sequences, and to include reference to the deposit information for clone Lyme21-9. As discussed in detail below, no new matter is added by the amendments to the specification.

Claim 16 is amended to conform it to current PTO practice regarding explicit recitation of nucleic acid and amino acid sequences. The amendment to claim 16 does not change the scope or content of the claim. New claims 38-49 are added to specifically recite embodiments of the presently claimed invention, and to recite a method of using the receptor of the invention. Support for new claims 38-44 comes from the specification, as originally filed, at pages 2-3, page 7, page 19, and Figure 1, for example. Support for new claims 45-49 comes from the specification, as originally filed, at pages 5-6, for example. Accordingly, no new matter is added by the amendment of claim 16, and new claims 38-49.

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I. *New Sequence Listing*

A new Sequence Listing is submitted herewith. The new Sequence Listing corrects three errors in original SEQ ID NO:1, which resulted in one error in original SEQ ID NO:2. The errors in original SEQ ID NO:1 are as follows:

1) original SEQ ID NO:1 contained a "g" (guanine) base at position 856. This base is, in fact, a "c" (cytosine) in clone Lyme21-9;

2) original SEQ ID NO:1 contained a "c" (cytosine) at position 1123. This base is, in fact, a "g" (guanine) in clone Lyme21-9; and

3) original SEQ ID NO:1 contained a "c" (cytosine) at position 1124. This base is, in fact, a "g" (guanine) in clone Lyme21-9.

Error "1)" in SEQ ID NO:1 did not result in an error in SEQ ID NO:2. Base 856 corresponds to the third position in the codon encoding amino acid residue 156 of SEQ ID NO:2. Because both the codon presented in the original Sequence Listing ("cgg") and the correct codon ("cgc") code for Arginine, no change in the amino acid sequence of SEQ ID NO:2 occurred due to correction of this error in SEQ ID NO:1.

Error "2)" in SEQ ID NO:1 did not result in an error in SEQ ID NO:2. Base 1123 corresponds to the third position in the codon encoding amino acid residue 245 of SEQ ID NO:2. Because both the codon presented in the original Sequence Listing ("gcc") and the correct codon ("gcg") code for Alanine, no change in the amino acid sequence of SEQ ID NO:2 occurred due to correction of this error in SEQ ID NO:1.

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Error "3)" in SEQ ID NO:1 discussed above created an error in SEQ ID NO:2. Base 1124 corresponds to the first position in the codon encoding amino acid residue 246 of SEQ ID NO:2. A change from the codon disclosed in original SEQ ID NO:1 ("cgc") to the correct codon in Lyme21-9 ("ggc") converts the codon from one coding for Arginine to one coding for Glycine. Correction of this error in SEQ ID NO:1 necessitated correction of the corresponding amino acid in SEQ ID NO:2.

As stated in the attached Declaration of Dr. Owman and Dr. Bristulf, the errors in the originally disclosed sequences of SEQ ID NO:1 and SEQ ID NO:2 were merely errors in the sequencing process that were unintended. It is known in the art that such errors often occur when performing manual sequencing using Sanger's dideoxynulceotide sequencing method. As stated in the Declaration, the errors were discovered when Dr. Bristulf re-sequenced the areas using automated sequencing apparatus. Because the errors in the originally-disclosed sequences resulted from shortcomings that are inherent to the technique used to sequence the Lyme21-9 nucleic acid, no deceptive intent accompanied the erroneous reporting of the sequences of SEQ ID NO:1 and SEQ ID NO:2.

The new Sequence Listing also eliminates SEQ ID NO:17, which was present in the original Sequence Listing. SEQ ID NO:17 was a duplicate of SEQ ID NO:2. Thus, it was redundant and unnecessary.

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II. *Deposit of Plasmid Clone Lyme21-9*

Plasmid clone Lyme21-9, originally disclosed in the application as filed, and containing the coding sequence for the CMKRL1 heptahelix receptor of this invention, has been deposited by the inventor, Dr. Christer Owman, at the American Type Culture Collection ("ATCC"; 10801 University Blvd., Manassas, VA 20110-2209). It was assigned accession number PTA-4543 by the ATCC. The specification has been amended at page 7 to include information relating to the deposit, in accordance with 37 C.F.R. § 1.809(d) and MPEP § 2406.01.

Proof of deposit of plasmid clone Lyme21-9 is provided in two documents attached to this Second Supplemental Preliminary Amendment. The first document is a receipt from the ATCC, indicating that plasmid clone Lyme21-9 was received by the ATCC, and would be maintained by the ATCC and the depositor, in accordance with the Budapest Treaty. The second document is a Deposit Declaration, executed by the inventor, Dr. Christer Owman, stating that plasmid clone Lyme21-9 was deposited with the ATCC, and will be maintained, in accordance with the Budapest Treaty and PTO rules governing deposits of biological materials.

U.S. patent regulations (37 C.F.R. § 1.804(b)) and PTO rules (MPEP § 2604.02) require that, when a deposit of a biological material is made after the effective filing date of the application, someone must corroborate that the deposited material is the material identified in the application. Because the Lyme21-9 clone was deposited after the effective filing date of this application, this requirement applies to the present application. Applicant is currently attempting to identify a person who may execute a Declaration in accordance with 37 C.F.R. § 1.804(b).

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Applicant affirms that he will submit the Declaration as soon as it has been prepared and executed.

III. *35 U.S.C. § 112, first paragraph*

Although not subject to any rejection at this time, in an effort to expedite allowance of the present claims, Applicant takes this opportunity to establish compliance of the specification and claims with 35 U.S.C. § 112, first paragraph.

U.S. law permits an applicant to deposit biological material necessary for practicing the claimed invention after the effective filing date (*e.g.*, priority date) of the application. According to PTO examination guidelines, deposit of the material satisfies all of the requirements of 35 U.S.C. § 112, first paragraph. MPEP § 2406. Accordingly, under PTO guidelines, deposit of the Lyme21-9 clone provides "enablement" and "written description" for the Lyme21-9 clone.

Under U.S. law, post-filing date deposit of biological material, and inclusion of information relating to that deposit, does not constitute "new matter". *In re Lundak*, 773 F.2d 1216, 1223 (Fed. Cir. 1985). Thus, amending the specification to include information relating to deposit of the Lyme21-9 clone does not raise any issues of "new matter" under the "written description" requirement of 35 U.S.C. § 112, first paragraph. *Id.*

Furthermore, under U.S. law, deposit of a clone containing one or more claimed sequences is sufficient to provide written description support for the claimed sequences:

> reference in the specification to a deposit in a public depository, which makes its contents accessible to the public when it is not otherwise available in written form, constitutes an adequate description of the deposited material sufficient to comply with the written description requirement of § 112, ¶ 1.

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Enzo Biochem Inc. v. Gen-Probe Inc., 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002). More specifically, in *Enzo*, the patentee-plaintiff deposited various nucleic acid probes in the ATCC in the form of recombinant DNA molecules within *E. coli* host bacteria. *Id.* at 1610. The defendant asserted that such a deposit was insufficient to provide a written description of the nucleic acid sequences of the probes, and thus the claims of the patent were invalid for failure to satisfy the "written description" requirement of 35 U.S.C. § 112, first paragraph. The Federal Circuit disagreed with the defendant, stating unequivocally that "reference in the specification to deposits of nucleotide sequences describe those sequences sufficiently to the public for purposes of meeting the written description requirement. *Id.* at 1614.

Because the deposit of clone Lyme21-9 provides an adequate written description of the nucleotide sequence of the clone, the sequence of SEQ ID NO:1, as presented in the corrected Sequence Listing, finds adequate written description in the application, as originally filed, and thus does not constitute "new matter". Likewise, because the sequence of SEQ ID NO:2 is directly obtainable from SEQ ID NO:1, it too finds adequate written description in the application, as originally filed, and thus does not constitute "new matter".

For at least the reasons presented herein, correction of the Sequence Listing and amending of the specification and the claims does not raise any issues under 35 U.S.C. § 112, first paragraph.

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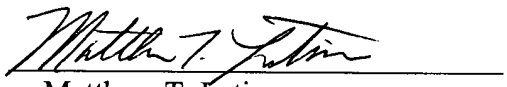
IV. *Conclusion*

Applicant respectfully submits that this application is in condition for examination on the merits. Therefore, prompt and favorable examination is requested. If the Office believes anything further is necessary in order to place this application in condition for examination, Applicant requests that his undersigned representative be contacted at the telephone number or e-mail address listed below.

Please grant any extensions of time required to enter this Second Supplemental Preliminary Amendment, and charge any required fees that are not submitted herewith to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: 

Matthew T. Latimer
Reg. No. 44,204
(571) 203-2714
matthew.latimer@finnegan.com

Date: February 19, 2003

Attachments:
Deposit Declaration
Receipt from ATCC
Declaration of Dr. Owman and Dr. Bristulf
Sequence Listing (paper and CRF)
Statement in Support of Sequence Listing

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APPENDIX

(accompanying Second Supplemental Preliminary Amendment of February 19, 2003)

09/893,512

IN THE SPECIFICATION:

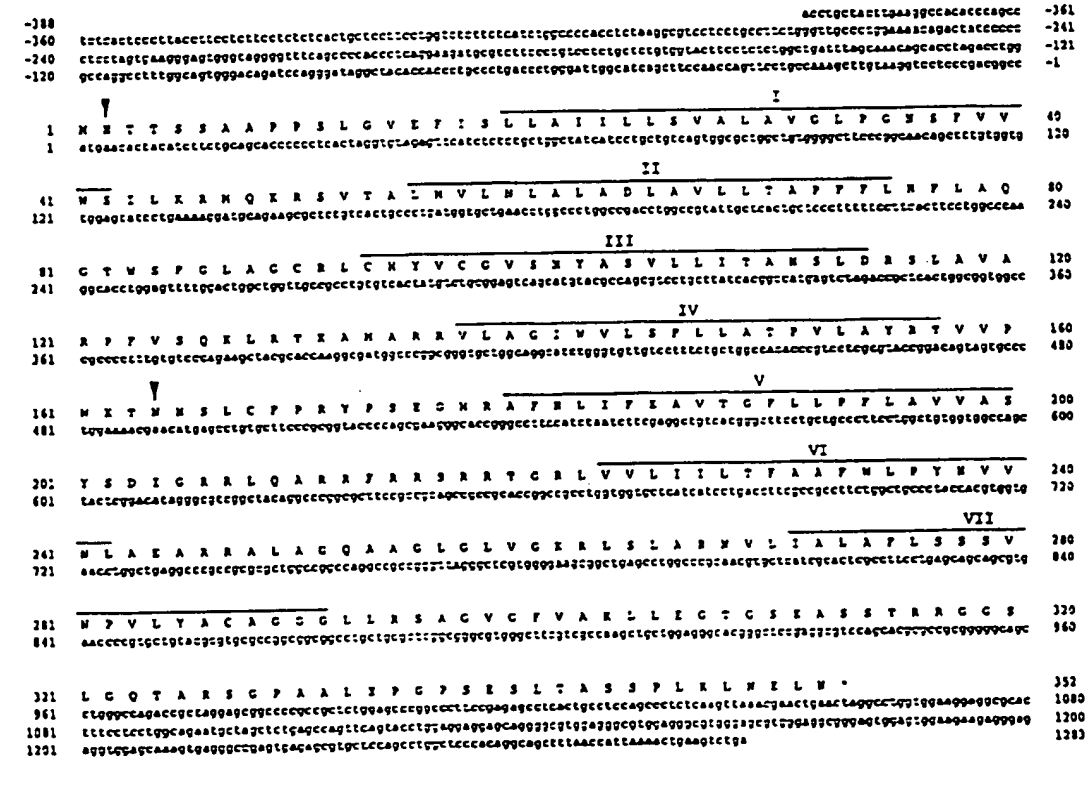
Please amend the specification as follows:

Page 4, replace the first paragraph with the following new paragraph:

-- In one embodiment of the invention, a heptahelix receptor of the invention has the [following] amino acid sequence of SEQ ID NO:2 and corresponding nucleotide [sequences:] sequence of

[

CLONING OF NOVEL HUMAN CHEMOATTRACTANT RECEPTOR



]

SEQ ID NO:1.--

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Page 7, replace the second full paragraph with the following three new paragraphs:

-- Figure 1 shows the nucleotide sequence (SEQ ID NO:1) of the coding region of Lyme21-9 and the deduced amino acid sequence (SEQ ID NO:2) of the corresponding human CMKRL1 receptor.

Plasmid clone Lyme21-9 was deposited on July 11, 2002, at the American Type Culture Collection ("ATCC"), 10801 University Blvd., Manassas, VA 20110-2209, in accordance with the Budapest Treaty, and was assigned accession number PTA-4543.

The first nucleotide and amino acid residue of the translation start site are designated as position 1. The putative transmembrane segments TMI-TMVII are indicated by solid lines; the extension of each segment is estimated on the basis of the hydrophobicity profile and sequence alignment of other heptahelix receptors. Potential glycosylation sites are indicated with arrowheads.--

Page 8, replace the first paragraph with the following new paragraph:

-- Figure 3 depicts the alignment of the complete amino acid sequences for eight human chemotactic receptors (SEQ ID NOs:9-16) together with the amino acid sequence deduced from the presently cloned cDNA (Lyme 21-9; SEQ ID NO:2) showing the high degree of similarity [(shaded areas)], not least within the transmembrane regions. The homology presentation was done with the SeqVu (version 1) mode in the GCG program. The scaling system used is described by Riek et al. (1995).--

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Replace the paragraph bridging pages 26 and 27 with the following new paragraph:

-- Sequence comparison with cloned receptors within the G-protein-linked superfamily showed most similarity with the subfamily of chemoattractant leukocyte receptors (Fig. 3), particularly the "classical" chemoattractants, C5a and *N*-formyl-methionyl-leucyl-phenylalanine (fMLP) (Fig. 4). For example, there is (in the GCG/fasta matrix score) an approximately 30% overall sequence identity with the human C5a anaphylatoxin receptor (Gerard and Gerard, 1991) and 28% identity with the fMLP receptor (Boulay *et al.*, 1990; Thomas *et al.*, 1990). Taken as a group together with the Lyme21-9 receptor cDNA clone (Fig. 3), there is a particularly high degree of consensus in the GN-LVVLV (SEQ ID NO:7) sequence motif in the TMI region and the LLNLA--DLLF--TLP-W (SEQ ID NO:8) motif within TMII.--

Replace the paragraph bridging pages 47 and 49 with the following new paragraph:

-- A cDNA library of a human B-cell lymphoblast cell line (GM03299; NIGMS Human Genetic Mutant Cell Repository, Camden, NJ) was constructed from poly(A)$^+$-selected RNA in the pcD/SP6/T7 cloning and expression vector (Morel *et al.*, 1992), a derivative of Okayama-Berg's pcD vector (Okayama *et al.*, 1987). The library contained 7.5 x 10^6 recombinants. Plasmid preparation was prepared by cesium chloride-ethidium bromide banding (Sambrook *et al.*, 1989) and used as template (1 µg) in PCR (Mullis and Faloona, 1987) attempting to amplify a DNA stretch between the putative TMII and TMVI of G-protein-coupled receptors. The sense primer was a 27-mer oligonucleotide with 250-fold degeneracy (5'- A(T)TCCTGGTG(C)A(T) G(A)CCTT(G)GCT(A)G(T)TGGCC(T)GAC-3' (SEQ ID NO:3)); the antisense primer was a 29-mer oligonucleotide with 128-fold degeneracy (5'- AT(G)GA(T)AGA(T)AGGGCAG

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CCAGCAGAC(G)C(G)G(A)T(C)GAA-3' (SEQ ID NO:4)). The primers were used in 1μM concentrations together with *Taq* polymerase (Genamp; Perkin-Elmer Cetus). Forty cycles of 96°C for 45 s (denaturation), 55°C for 4 min (annealing), and 72°C for 4 min (extension) were carried out, followed by a final extension at 72°C for 15 min. The products were analyzed on a 3% NuSieve genetic technology-grade agarose gel (FMC BioProducts). Three bands between 500 and 700 bp in size were excised and blunted with T4 polymerase, and terminal phosphates were added with T4 polynucleotide kinase (New England Biolabs). The fragments were subcloned into the *Hinc*II site of the M13mp18 vector and sequenced according to Sanger's dideoxynucleotide termination method. Several sequences exhibited homology with the G-protein-coupled superfamily. Sequence information from one insert (hLym10) was utilized to obtain a full-length cDNA clone.--

Replace the paragraph bridging pages 49 and 50 with the following new paragraph:

-- On the basis of sequence stretches in the PCR clone corresponding to the putative first extracellular and third intracellular loops, two 48-bp oligonucleotides were synthesized, one designated Lym5, 5'-ACACAGGAGGCAACCAGCCAGTCCAAAACTCCAGG TGCCTTGGGCCAG-3' (SEQ ID NO:5), and the other Lym6, 5'-GATCGGTGCCAGCA CCCGCCGGGCCATCGCCTTGGTGCGTAGCTTCTG-3' (SEQ ID NO:6). They were labeled with [γ-^{32}P]ATP (5000 Ci/mmol, Amersham) and used in combination as probes to screen pools of recombinants prepared from consecutive dilutions (Bonner *et al.*, 1987) of the human B-cell lymphoblast cDNA library. Hybridization of Southern blots was performed in 3 x SSC (0.45 M NaCl, 0.05 M sodium citrate, pH 7.0) at 60°C, and the filters were washed in 1 x SSC at the

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same temperature. A positive band of 1.7 kb in size was followed until a single clone (designated Lyme21-9) was obtained. Overlapping restriction fragments were subcloned into M13 phage vectors for sequencing of both cDNA strands. Sequence analysis and comparisons were performed with Genetics Computer Group software (University of Wisconsin) and with GenBank as well as with the GeneWorks program from IntelliGenetics (Mountain View, CA). Hydrophobicity tests of the deduced amino acid sequence were carried out according to Kyte and Doolittle (1982). Chromosome mapping results were evaluated in the Genome Data Base (GDB 6.0) and the NCBI database (Online Mendelian Inheritance in Man; OMIM).--

IN THE CLAIMS:

Please amend claim 16 as follows:

16. (Amended) [A] An isolated or purified heptahelix receptor having an amino acid sequence comprising the sequence[:

1	MNTTSSAAPPSLGVEFISLLAIILLSVALAVGLPGNSFVV	40
41	WSILKRMQKRSVTALMVLNLALADLAVLLTAPFFLHFLAQ	80
81	GTWSFGLAGCRLCHYVCGVSMYASVLLITAMSLDRSLAVA	120
121	RPFVSQKLRTKAMARRVLAGIWVLSFLLATPVLAYRTVVP	160
161	WKTNMSLCFPRYPSEGHRAFHLIFEAVTGFLLPFLAVVAS	200
201	YSDIGRRLQARRFRRSRRTGRLVVLIILTFAAFWLPYHVV	240
241	NLAEARRALAGQAAGLGLVGKRLSLARNVLIALAFLSSSV	280
281	NPVLYACAGGGLLRSAGVGFVAKLLEGTGSEASSTRRGGS	320
321	LGQTARSGPAALEPGPSESLTASSPLKLNELN (SEQ ID NO:2)	352

]

of SEQ ID NO:2.

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